



## Acquired Angioedema: A Herald of Malignancy

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### ABSTRACT

Acquired angioedema (AAE) is a rare condition whose origin lies in microcellular immunology. Although only 168 cases of AAE have been documented, the disorder appears to be commonly associated with malignant disease. This case report examines a patient who initially presented with AAE, but then developed a monoclonal gammopathy of undetermined significance (MGUS) that likely transformed into a B-cell lymphoma. The review of his medical chart covered a span of 15 years.

The increase in reported cases over the past 10 years has made the association of AAE with malignant disease more evident. This case in particular illustrates AAE as a surrogate marker of transformation in patients with MGUS. It also supports the notion that breakthrough AAE in a patient who had been well controlled should have a repeat investigation for malignant disease, or in our patient's case, malignant transformation.

### INTRODUCTION

Acquired angioedema (AAE) ultimately results from a deficiency of C1 esterase inhibitor (C1-INH), which is a hepatically produced protease inhibitor that serves as the regulator of the classical complement cascade, contact system, and intrinsic coagulation.<sup>1</sup> Its reduction provokes spontaneous hyperactivation of the complement and contact systems (C1-INH inhibits kallikrein, which indirectly causes bradykinin release), all of which result in angioedema.<sup>2-5</sup> First described by Caldwell in 1972, there have been 168 cases reported since.<sup>6</sup> We highlight a case of a patient who initially presented with AAE in 1998 and has been followed at our institution for the past 15 years.

### CASE STUDY

Our patient is a 79-year-old man who had his first episode of pharyngeal angioedema in May 1998, at which time his C4 level was also found to be undetectable. He subsequently had his second episode of facial angioedema in June 1998, and laboratory results at that time revealed a low C1-INH level plus a high C1q binding level. He was presumed to have AAE and underwent a thorough workup for malignancy, which included serum protein electrophoresis, urine protein electrophoresis, bone marrow biopsy, computed tomography of the chest and sinuses, and a liver/spleen nuclear medicine study, all of which were unremarkable. However, in July 1998, he was found to have a faint kappa light chain restriction in his urine by immunofixation electrophoresis. He was given a diagnosis of monoclonal gammopathy of undetermined significance (MGUS) and was referred to hematology/oncology, where he continues to be followed. The patient later had his third episode of pharyngeal angioedema in October 1998 with continued low C4 and C1-INH levels, and at that time he was started on attenuated androgens with danazol 200 mg twice daily.

Also of note in October 1998, an autoantibody test was sent to the National Jewish Health Complement Laboratory, which found normal limits for C1-INH free and bound IgG antibodies.

Importantly, our patient's AAE responded well to danazol, and his dose was weaned over time, until he had a breakthrough episode of angioedema in May 2000 after a dose reduction to 50 mg every other day. The danazol dose was increased to 100 mg every other day, and the patient remained stable for more than 12 years without any episodes of angioedema. Then in September 2012, the patient experienced an acute episode of angioedema, which resulted in a hospital admission. His danazol dose was increased to 100 mg once daily, and he was discharged after a period of observation without further workup. Approximately 5 months later in February 2013, our patient was admitted to the hospital for acute abdominal pain, which was determined to be secondary to gallstone pancreatitis. He was incidentally found to have splenomegaly with a white blood cell count (WBC) of 49,000 that was predominantly lymphocytic (64%, with 19% of those atypical lymphocytes). Peripheral smear revealed atypical lymphocytic cells, and flow cytometry demonstrated CD5 negative, CD10 negative kappa-restricted B lymphocytes. Subsequent bone marrow biopsy confirmed a B-cell lymphoproliferative process consistent with stage IV splenic marginal zone lymphoma plus villous lymphocytes (SMZL).

The patient underwent 6 weeks of chemotherapy with rituximab. This resulted in a complete bone marrow response without any evidence of residual B-cell lymphoma plus normal fluorescence in situ hybridization. Also, he had partial resolution of splenomegaly (14 cm in anteroposterior diameter and 12 cm craniocaudal, previously 20 cm in anteroposterior diameter and 19 cm craniocaudal), and normalization of peripheral WBC



counts. Additionally, the serum free light kappa/lambda chains decreased after chemotherapy. He continues to be monitored closely.

## DISCUSSION

AAE is characterized by low C1-INH (<50% of normal), C1q, and C4 in the setting of either MGUS, lymphoproliferative disease, autoantibodies, or any combination of the aforementioned. The stark difference between hereditary angioedema (HAE) and AAE is the low C1q, absence of angioedema in family members, and presentation of symptoms in the fourth or fifth decade of life.<sup>8</sup> The low levels of C1-INH in AAE readily increase activation of complement/contact systems, thus producing local increase in vascular permeability of the skin and gastrointestinal/oropharyngeal mucosa.

AAE was initially classified into 2 types, with type I associated with B-cell lymphoproliferative diseases, and type II associated with C1-INH autoantibodies that seemingly are often linked with paraproteinemias.<sup>2</sup> However, the current consensus dismisses this dual classification, as most AAE cases have overlapping features of both types.<sup>6</sup> Regardless, the centralizing theme with AAE and our case in particular is its overall association with malignancy. This was shown in a study of 42 patients with AAE conducted in 1996, which found that 33 of the patients had C1-INH autoantibodies and 32 of those 33 patients had later developed either MGUS or non-Hodgkin lymphoma.<sup>7</sup>

## SUMMARY

Our case further bolsters the association of AAE with malignancy. It is unlikely to be a coincidence that our patient, who had been well controlled for many years on the same dose of danazol, suddenly presented with an episode of angioedema 5 months prior to SMZL being diagnosed. It is worth noting that cells from both the patient's MGUS and the SMZL were found to be kappa restricted, suggesting clonality or that these disease processes were from the same B-cell lineage. We believe it is possible that our patient's clinical change represented a progression of his underlying MGUS. Our case supports the need for a repeated malignancy evaluation in a previously stable patient with AAE who experiences a breakthrough episode of angioedema while on therapy.

## REFERENCES

1. Fiechtner JJ, Marx JJ, Wolski KP, et al. Acquired angioedema, autoimmune hemolytic anemia, and lymphoma: resolution after therapy. *J Clin Immunol Immunopathol.* 1980;15:642-645.
2. Zanichelli CM. The acquired deficiency of C1-inhibitor: lymphoproliferation and angioedema. *Curr Mol Med.* 2010;10:4:1875-1876.
3. Lang DM, Werner A, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol.* 2012;109:395-402.
4. Lam DH, Levy NB, Nickerson JM, et al. Acquired angioedema and marginal zone lymphoma. *J Clin Oncol.* 2012;30:16:e151-e153.
5. Phanish MK, Owen A, Parry DH. Spontaneous regression of acquired C1 esterase inhibitor deficiency associated with splenic marginal zone lymphoma presenting with recurrent angioedema. *J Clin Pathol.* 2002;55:789-790.
6. Lin JH, Cassillas AM, Sattar S. C1-esterase inhibitor autoantibodies in a patient with acute tongue swelling. *Allergy Asthma Proc.* 2007;28:93-96.
7. Cicardi M, Beretta A, Colombo M, et al. Relevance of lymphoproliferative disorders and of anti-C1 inhibitor autoantibodies in acquired angioedema. *J Clin Exp Immunol.* 1996;10:475-480.
8. Breitbart SI, Bielory L. Autoantibody associations and C1q utility as a diagnostic tool. *Allergy Asthma Proc.* 2010;31:428-434.

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